The SafeBoosC phase II randomised clinical trial: a treatment guideline for targeted near-infrared-derived cerebral tissue oxygenation versus standard treatment in extremely preterm infants

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Abstract: UNLABELLED: Near-infrared spectroscopy-derived regional tissue oxygen saturation of haemoglobin (rStO2) reflects venous oxygen saturation. If cerebral metabolism is stable, rStO2 can be used as an estimate of cerebral oxygen delivery. The SafeBoosC phase II randomised clinical trial hypothesises that the burden of hypo- and hyperoxia can be reduced by the combined use of close monitoring of the cerebral rStO2 and a treatment guideline to correct deviations in rStO2 outside a predefined target range. AIMS: To describe the rationale for and content of this treatment guideline. METHODS: Review of the literature and assessment of the quality of evidence and the grade of recommendation for each of the interventions. RESULTS AND CONCLUSIONS: A clinical intervention algorithm based on the main determinants of cerebral perfusion-oxygenation changes during the first hours after birth was generated. The treatment guideline is presented to assist neonatologists in making decisions in relation to cerebral oximetry readings in preterm infants within the SafeBoosC phase II randomised clinical trial. The evidence grades were relatively low and the guideline cannot be recommended outside a research setting.

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The SafeBoosC Phase II Randomised Clinical Trial: A Treatment Guideline for Targeted Near-Infrared-Derived Cerebral Tissue Oxygenation versus Standard Treatment in Extremely Preterm Infants

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Key Words

Near-infrared spectroscopy · Newborn · Practice guideline · Cardiovascular agents · Hypotension · Oxygen consumption · Carbon dioxide · Hyperoxia

Abstract

Near-infrared spectroscopy-derived regional tissue oxygen saturation of haemoglobin ($rStO_2$) reflects venous oxygen saturation. If cerebral metabolism is stable, $rStO_2$ can be used as an estimate of cerebral oxygen delivery. The SafeBoosC phase II randomised clinical trial hypothesises that the burden of hypo- and hyperoxia can be reduced by the combined use of close monitoring of the cerebral $rStO_2$ and a treatment guideline to correct deviations in $rStO_2$ outside a predefined target range. ***Aims:*** To describe the rationale for and content of this treatment guideline. ***Methods:*** Review of the literature and assessment of the quality of evidence and the grade of recommendation for each of the interventions. ***Results and Conclusions:*** A clinical intervention algorithm based on the main determinants of cerebral perfusion-oxygenation changes during the first hours after birth was gen-

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erated. The treatment guideline is presented to assist neonatologists in making decisions in relation to cerebral oximetry readings in preterm infants within the SafeBoosC phase II randomised clinical trial. The evidence grades were relatively low and the guideline cannot be recommended outside a research setting.

Introduction

Abnormal haemodynamic adaptation during the transitional circulation together with the impact of respiratory distress syndrome and related factors on blood flow distribution [1] cause abnormalities in cerebral haemodynamics and oxygen supply [2–4]. Near-infrared spectroscopy (NIRS)-derived regional tissue oxygen saturation of haemoglobin ($rStO_2$) is an absolute value corresponding to mixed blood saturation, and can be used as a surrogate measure for venous oxygen saturation [5]. This allows the derivation of several variables related to tissue oxygen dynamics, such as oxygen delivery and consumption and the ratio between oxygen delivery to oxygen extraction, the so-called cerebral fractional oxygen extraction (FOE) [5, 6]. Theoretically, therefore, this monitoring system could help to adjust interventions with effects on blood and oxygen supply to the brain.

The SafeBoosC phase II randomised clinical trial hypothesises that the burden of hypo- and hyperoxia can be reduced, and consequently the risk of brain injury, by the combined use of close monitoring of the cerebral $rStO_2$ and an evidence-based treatment guideline to correct deviations in $rStO_2$ outside a predefined target range [7–9]. Accordingly, a treatment guideline has been developed focusing on interventions that could have an impact on arterial oxygen saturation (SaO_2), haemoglobin concentration, and cerebral blood flow (CBF), which are the main determinants of oxygen delivery to the brain. The purpose of this report is to describe the rationale for this treatment guideline and the treatment recommendations.

Interventions That Affect Oxygen Delivery to the Brain

In drawing up the treatment guideline we used the premise that hypoxia and hyperoxia are risk factors for an adverse outcome in the preterm infant and should be avoided [10–15]. In addition to NIRS assessment of the cerebral circulation, a number of other techniques, particularly echocardiography, are used to assess the neonatal transitional circulation and related outcomes [1, 16–27]. For the purposes of the treatment guideline, a systematic review of the literature was carried out focusing on clinical studies conducted on human neonates that used NIRS-derived variables as outcome measures supporting the statements listed in the treatment guideline for intervention in the SafeBoosC phase II randomised clinical trial. The literature review was conducted in March 2011 using the database PubMed and subject headings (MeSH terms). There were no date restrictions. The search board was kept to combine the concept of a neonate (or newborn) with the concepts of NIRS and cerebrovascular circulation. In addition, blood pressure, hypotension, dopamine, dobutamine, epinephrine, anaemia, blood transfusion, carbon dioxide, respiratory distress syndrome, patent ductus arteriosus (PDA) and treatment, and blood glucose were also combined with the terms NIRS and newborn. This search was supplemented by cross references. Two hundred and twenty-nine abstracts were selected for review; among them, only 27% were relevant for the issues to be addressed in the treatment guideline. Only 4% of the selected studies were randomised clinical trials.

The proposed treatment guideline for the SafeBoosC phase II randomised clinical trial is based on interventions that may optimise cerebral oxygen supply and consumption through factors such as perfusion pressure, ventricular output, arterial oxygen content, arterial carbon dioxide, or blood glucose concentration. We assume a rather steady cerebral metabolic rate of oxygen. Given that the SafeBoosC intervention period focuses on the first 3 days after an extremely low gestational age neonate is born [8, 9], disease states and related factors most commonly present during that period were of particular interest. The definition of normal range for cerebral $rStO_2$ in this trial (55–85%) was derived from Lemmers and van Bel [unpubl. data] as the 95% CI of $rStO_2$ monitoring of 439 preterm infants born at <32 weeks during the first 3 days after birth using INVOS and the Adult SomaSensor (Somanetics-Covidien, Dublin, Ireland). The application of the adult sensor in this population is considered safe as no serious adverse device effects, such as skin burns, were found in these infants. Device eligibility will be tested by comparison of absolute values, reproducibility, and sensitivity to changes in oxygenation on the adult arm [28]. Absolute values and dynamic range within 5 percentage points of INVOS and reproducibility better than 6% are the predefined thresholds. So far, eligible devices for the SafeBoosC trial include INVOS 5100C with the Adult

SomaSensor, NIRO 200NX (Hamamatsu Photonics, Fukuoka, Japan) with a small probe holder, and OxyPrem, a prototype developed by investigators in the SafeBoosC trial (M.W.).

We developed a pathophysiologically oriented, evidence-based treatment guideline and assessed the level of recommendation according to the US Preventive Services Task Force (USPSTF) System from 2001 [29] (Appendix). A new version of the USPSTF system is currently in use [30] where the wording of the grade C recommendation is possibly the most important change with respect to the previous version; it reads: '... against routinely providing X service for Y population; there may be considerations that support providing the service in an individual patient'. One of the actions listed in the present treatment guideline (i.e. volume expansion with normal saline) has been classified as a grade C recommendation. This, as well as the remaining actions included, is a suggested but not mandated intervention, and all of them should be considered individually according to the patient's overall clinical condition. Newer developments for grading the quality of evidence and the strength of recommendations [31] are more rigorous, but also more complex and time consuming. We, therefore, adhered to the USPSTF system due to its relative ease of use.

If $rStO_2$ falls out of the normal range (55–85%) and there is no reason to believe that it will normalise without an intervention, this treatment guideline aims to bring a standardised approach to correct the deviation. As the effect of certain interventions, such as the effect of cardiovascular drugs on blood pressure, are not expected to be immediate, it is recommended to choose only one intervention at a time and reassess after 30–60 min. It must be kept in mind that many routine care-giving procedures in the neonatal intensive care unit, such as handling or change in posture [32, 33], endotracheal tube repositioning or suctioning [32], or blood sampling from umbilical lines [34–36], among others, may have an impact on cerebral haemodynamics and oxygenation. However, since NIRS changes determined by these factors are usually transient and can be anticipated, they have not been listed in this treatment guideline.

Online supplementary figure 1 (for all online suppl. material, see www.karger.com/doi/1159/000351346) shows an algorithm that describes the flow of suggested interventions in the SafeBoosC trial when $rStO_2$ is out of the target range.

$rStO_2$ below the threshold may reflect compromised oxygen delivery. The proposed interventions are directed to increasing CBF, oxygen transport capacity, or blood oxygen content. Accordingly, the assessment of cardiovascular status, haemoglobin concentration, and SaO_2 should be done before an intervention is chosen.

Assessment/Interventions Related to Cardiovascular Status

Changes in $rStO_2$ or FOE may follow changes in cerebral perfusion pressure in infants with haemodynamic instability, which may [37–39] or may not [40–42] be reflected by concordant changes in mean arterial blood pressure. Thus, this treatment guideline would suggest to check the cardiovascular system, primarily considering clinical variables available in routine clinical practice, such as blood pressure, blood lactate concentration, capillary refill time, or urine output to define whether compromised systemic circulation is present or not. Echocardiography-derived variables on blood flow distribution, such as cardiac output and superior vena cava flow measurements, may be of value as complementary assessments to indicate or guide intervention.

Administration of fluid bolus, vasopressor-inotropes (dopamine or epinephrine), or inotropes (dobutamine), has a variable effect on blood pressure, cardiac performance, and cerebral perfusion-oxygenation [16–20, 43]. The effect of volume expansion on $rStO_2$ has not been systematically explored in infants. However, a recent randomised clinical trial has shown that delayed cord clamping increases cerebral $rStO_2$ at 4 and 24 h after birth in preterm infants [44]. This early increase in preload possibly ameliorates cardiovascular maladaptation during transitional circulation [45].

Studies in neonates have shown that dopamine [38, 43] and epinephrine [43], given to treat early systemic hypotension, increase cerebral perfusion-oxygenation. The 2-year follow-up of the study population showed comparable outcomes in vasopressor-inotrope-treated infants and infants who did not develop hypotension and thus did not receive cardiovascular support early after birth [16]. However, cautious use of vasopressors is recommended, as increased afterload may further compromise myocardial contractility causing additional decrease in cardiac output [1], and consequently, worsening cerebral perfusion.

The effect of a haemodynamically significant PDA or its treatment on cerebral haemodynamics and oxygenation is addressed in a number of studies using NIRS and other monitoring methods [46–61]. PDA may be a determinant in blood flow redistribution causing decreased blood pressure and rStO2 and increased FOE [57]. However, no correlation was found between ductal size and

$rStO_2$ [60]. Treatment of PDA may also be relevant for the $rStO_2$ [57]. Indomethacin has been shown to have an acute greater impact on cerebral perfusion and oxygenation [47, 49, 52, 58, 59] than ibuprofen [51, 52]. However, slower infusion rates did not have such an impact on brain haemodynamics [61]. Surgical closure of the PDA showed no consistent effects on cerebral circulation and oxygenation [53–56].

Finally, mechanical factors, particularly lung overinflation, may decrease preload and cause increased pulmonary vascular resistance. Both factors would impair myocardial function and cardiac output [22–25]. This condition should always be ruled out in case of decreasing $rStO_2$.

Assessment/Interventions Related to Oxygen Transport (Blood Oxygen Carrying Capacity)

Although there is no clear correlation between haemoglobin concentration and tissue oxygen extraction [62, 63], packed-red cell transfusion improves cerebral oxygenation in the anaemic preterm infant [63–65]. In addition, a randomised clinical trial has shown that placental-to-foetal transfusion increases $rStO_2$ [44], possibly not only due to increased oxygen carrying capacity but also to improved preload. A positive effect of this procedure on superior vena cava flow has been recently reported [45].

Assessment/Interventions Related to Respiratory Status

Infants with respiratory distress syndrome have a significantly larger range of cerebral $rStO_2$ and FOE and a stronger relation between these cerebral haemodynamic variables and mean arterial blood pressure than infants without respiratory distress syndrome [66]. One of the most important determinants of CBF and cerebral oxygen dynamics is partial pressure of carbon dioxide (PCO_2) [46, 63, 67–70]. It is crucial, because inadvertent hyperventilation may occur as a result of mechanical ventilation during the acute phase of respiratory distress syndrome. If PCO_2 is below the normal range or low, even in the normal range, we recommend considering to decrease minute ventilation in case of low $rStO_2$ [63, 67–69]. Since the effect of manipulating minute ventilation on $rStO_2$ has not been tested in a randomised trial, the evidence level in this guideline is only II. The understanding of the mechanics and physiology, as well as the epidemiological link between hyperventilation and brain injury and cerebral palsy, however, may be seen as sufficient for a stronger recommendation (A).

The effect of the type of mechanical ventilation or airway pressure on the cerebral haemodynamics and oxygenation by NIRS has been the focus of some small observational studies in newborns [71–75]. The way these different methods affect intrathoracic pressures would likely impact the cerebral and systemic circulation of immature neonates [76].

This treatment guideline has been modified after a pilot trial [77] to specifically warn against exceeding the upper threshold of SaO_2 according to local policies. Therefore, the fractional inspired oxygen fraction (FiO_2) should only be increased if SaO_2 is below the normal range or low, even in the normal range [10]. Other potential actions relate to increasing SaO_2 through improvement in lung recruitment by moderate increase in mean airway pressure [22, 26, 75].

$rStO_2$ increasing above the upper normal limit may reflect impaired oxygen utilisation or disturbed cerebral autoregulation, and interventions should be directed at decreasing hyperaemia. The assessment of respiratory status and blood glucose content should be done before an intervention is chosen.

Assessment/Interventions Related to Respiratory Status

The first step would be decrease FiO_2 in case SaO_2 is above the normal range or high, even in the normal range [11–15]. Additional interventions would be to decrease mean airway pressure [26, 75]. The vasodilator effect of PCO_2 should be considered, so minute ventilation should be increased in case of PCO_2 above the normal range or high, even in the normal range, to lower PCO_2 [63, 67–69].

Assessment of Blood Glucose Level

Hypoglycaemia would be the cause of capillary recruitment and increased CBF [27, 78]. Thus, if the blood glucose level is below the normal range or low, even in the normal range, increased glucose intake should be considered to raise blood glucose concentration.

Conclusion

This treatment guideline for the SafeBoosC phase II trial aims to help neonatologists to take decisions in relation to cerebral oximetry readings. None of the suggested actions are mandatory. The proposed clinical intervention algorithm is focused on the main determinants of cerebral perfusion-oxygenation changes during the first hours after birth in the extremely low gestational age neonate population, and is thus pathophysiologically

oriented. The evidence supporting some of these statements is generally rather weak. The proposed interventions, however, are all routinely used in clinical care of these patients. Particular care has been taken on hyperventilation with low PCO_2 and oxygen administration with high SaO_2 due to their association with adverse outcomes. We stress that this guideline is not approved for general use outside randomised clinical trials. We look forward to be able to report the results of the present SafeBoosC phase II randomised clinical trial and the planned SafeBoosC phase III randomised clinical trial that will evaluate the combined effect of NIRS and this treatment guideline [8, 9].

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Disclosure Statement

The authors have no potential conflict of interest.

Appendix

SafeBoosC Trial Treatment Guideline

$rStO_2$ <55%

Assess cardiovascular status
Blood pressure below the normal range or low, even in the normal range, consider:
- Vasopressor-inotropes (I/B) [16, 43]
- Fluid bolus (normal saline) (I/C) [17, 18]
- Decrease mean airway pressure (III/B) [22–25]

Poor systemic circulation, consider if:
Echocardiography shows low cardiac output and/or low superior vena cava flow
- Inotropes (I/B) [18–20, 40–42]
- Fluid bolus (normal saline) (I/C) [17, 18]
- Decrease mean airway pressure (III/B) [22–25]
- Reduce vasopressor (III/B) [1]

Echocardiography not available but has at least two of the following signs:
- Lactate >3.5 mmol/l
- CRT >3 s
- Urine output <1 ml/kg/h

Consider:
- Inotropes (I/B) [18–20, 40–42]
- Fluid bolus (normal saline) (I/C) [17, 18]
- Decrease mean airway pressure (III/B) [22–25]
- Reduce vasopressor (III/B) [1]

PDA, consider:
- Medical treatment (II-2/B) [21, 23, 24, 57]

Assess oxygen transport
Haemoglobin below the normal range or low, even in the normal range, consider:
- Red blood cell transfusion (I/B) [44, 63–65]

Assess respiratory status
SaO_2 below the normal range or low, even in the normal range, consider:
- Increase FiO_2 (II-1/A) [10] (attention: be careful not to exceed the upper target threshold of SaO_2)
- Increase mean airway pressure (III/B) [22, 26, 75]

PCO_2 below the normal range or low, even in the normal range, consider:
- Decrease minute ventilation (II-2/A) [63, 67–69]

$rStO_2$ >85%

Assess respiratory status
SaO_2 above the normal range or high, even in the normal range, consider:
- Decrease FiO_2 (II-2/A) [11–15]
- Decrease mean airway pressure (III/B) [26, 75]

PCO_2 above the normal range or high, even in the normal range, consider:
- Increase minute ventilation (II-2/A) [63, 67–69]

Assess blood glucose level
Blood glucose <2.5 mmol/l, consider:
- Increase glucose intake (II-2/A) [27, 78]

The recommendation according to the US Preventive Services Task Force (USPSTF) System for 20001 [29]. The Roman number refers to the level of evidence hierarchy the recommendation originates from (I; II-1; II-2; II-3; III) and the letter is our recommendation according to the USPSTF grading (A; B; C; D; I).

Level of evidence	Type of study
I	evidence obtained from at least one properly randomised controlled trial
II-1	evidence obtained from well-designed controlled trials without randomisation
II-2	evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group
II-3	evidence obtained from multiple time series with or without intervention; dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) can also be regarded as this type of evidence
III	opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees

Quality of evidence	Net benefit			
	substantial	moderate	small	zero/negative
Good	A	B	C	D
Fair	B	B	C	D
Poor = I				
Standard recommendation language	A = strongly recommended (good evidence that the intervention improves important health outcomes and benefits substantially outweigh harms)			
	B = recommended (at least fair evidence that the intervention improves important health outcomes and benefits substantially outweigh harms)			
	C = no recommendation for or against routine provision of the intervention (fair evidence that the service can improve health outcomes but the balance of the benefits and harms is too close to justify a general recommendation)			
	D = recommends against routinely providing the intervention (at least fair evidence that the service is ineffective or that harms outweigh benefits)			
	I = insufficient to recommend for or against routinely providing the intervention (evidence that the intervention is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined)			

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